

Risk factors for postoperative complications after elective ileocolic resection for Crohn's disease: a retrospective study

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Abstract

Background The incidence of postoperative complications (POC) in patients with Crohn's disease (CD) who undergo intestinal resection is high. The literature provides conflicting data about the risk factors for POC, especially regarding preoperative immunosuppressive medications. The purpose of this study was to evaluate the impact of anti-tumor necrosis factor (TNF) agents on the postoperative course and identify other predictors for POC after ileocolic resection (ICR).

Methods This was a single-center retrospective study that included 153 CD patients who underwent elective ICR in a Greek tertiary center between January 2010 and December 2018. Risk factors for overall POC and intra-abdominal septic complications (IASC) were assessed with univariate and multivariate analyses.

Results Overall POC and IASC occurred in 35 (22.9%) and 19 (12.4%) patients, respectively. In multivariate analysis, anti-TNF agents (n=61), as either monotherapy or combination treatment, were not associated with an increased risk for overall POC (21.3% vs. 23.9%, P=0.71) or IASC (13.1% vs. 12.0%, P=0.83). Similarly, no combined immunosuppressive regimen significantly correlated with POC. Patients with perianal disease, disease duration >10 years, or previous intestinal resections had significantly higher rates of both overall POC and IASC. In multivariate analysis, previous resection was the only independent risk factor for overall POC (odds ratio [OR] 3.90, 95% confidence interval [CI] 1.38-11.06; P=0.010) and IASC (OR 4.56, 95%CI 1.51-13.77; P=0.007).

Conclusions Preoperative administration of anti-TNF agents or other immunosuppressive regimens was not a risk factor for total POC or IASC. A history of previous resection independently correlated with both overall POC and IASC.

Keywords Crohn's disease, postoperative complications, intra-abdominal septic complications, anti-TNF, previous resections

Ann Gastroenterol 2020; 33 (6): 645-655

Introduction

Crohn's disease (CD) is a chronic inflammatory condition that follows a course of alternating periods of relapse and remission and can affect any part of the gastrointestinal tract [1]. In 1998, the approval of infliximab, the first monoclonal antibody against tumor necrosis factor (TNF)- α , changed the

modern conservative treatment of inflammatory bowel diseases (IBD) [2]. Despite immense progress in the era of biologic agents regarding the medical treatment of CD, the need for intestinal resection remains high: at 1, 5 and 10 years after diagnosis the risk for intestinal surgery is 16%, 33% and 47%, respectively [3].

Current evidence suggests high rates for postoperative complications (POC); up to 37% of CD patients who undergo surgery will experience POC [4]. Thus, several studies have tried to highlight the risk factors related to POC and research has been mainly focused on the preoperative immunosuppressive medication as a potential predictor of POC. However, the majority of current data regarding the association between medication and POC are extracted from observational, retrospective studies with high heterogeneity regarding POC classification (overall, anastomotic-related, septic vs. non-septic, minor vs. major), medication dosage, interval between last administration and surgery, and the examination of confounding factors such as nutritional status

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Conflict of Interest: None

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Received 3 May 2020; accepted 29 June 2020; published online 16 September 2020

DOI: <https://doi.org/10.20524/aog.2020.0533>

or coadministration of other immunosuppressive regimens [5]. Another confounding factor that should be taken into account is surgery in the emergency/urgent setting. These patients cannot be properly optimized preoperatively in order to minimize the risk for postoperative morbidity [6].

While the findings for certain categories of medication, such as steroids or immunomodulators (IM), are highly consistent in the literature [7,8], data regarding biologic agents remain conflicting [9]. The purpose of this study was to evaluate the impact of anti-TNF therapy on the postoperative course and to identify other risk factors for overall and intra-abdominal septic POC in CD patients who undergo elective ileocolic resection (ICR).

Patients and methods

Patient selection

This was a single-center retrospective study based on a prospectively updated database of 218 CD patients who underwent ICR with primary anastomosis in a tertiary referral center between January 2010 and December 2018. Exclusion criteria were age <18 years, defunction of the anastomosis with a proximal diverting ileostomy, emergency or urgent surgery, and missing or invalid data precluding analysis. Patients who simultaneously had small bowel resection or segmental colectomy or strictureplasty, apart from ICR, were included in the cohort. After these exclusion criteria were applied, 153 patients were eligible for analysis. This study was approved by the hospital's research and ethics committee.

Preoperative data and management

Data were retrieved using either the prospectively updated electronic IBD database or the patients' hospital medical records. Demographic variables included age, sex, smoking habit, body mass index (BMI) according to the World Health Organization (WHO) classification [10], and the American Society of Anesthesiologists (ASA) physical status score [11]. Disease phenotype was recorded according to the Montreal classification for CD [12]. Further disease characteristics included disease duration, previous intestinal resections, and the presence of extraintestinal manifestations. Preoperative serum albumin (g/dL) and hemoglobin (g/dL) were also recorded; the cut-off value of 3.0 g/dL was used to discriminate low albumin concentration [13], while the severity of anemia was categorized according to WHO classification [14]. Intraoperative data included surgical approach (open vs. laparoscopic), concomitant intestinal resection or strictureplasty, and anastomotic configuration.

The administration of 5-aminosalicylates, IM (azathioprine, 5-mercaptopurine, methotrexate), and steroids in the timeframe of 4 weeks before surgery was recorded; there is inconsistency in the literature regarding the interval between

last dose and surgery, ranging from 4-12 weeks, in order for a patient to be considered exposed to immunosuppressive treatment [15-17]. For the purposes of the present analysis, patients who received anti-TNF or other biologic agents within 3 months before resection were considered positive; this is in accordance with many previous studies [15,16]. Furthermore, the therapeutic regimens were classified according to whether patients were under monotherapy or combination treatment (≥ 2 categories of medications).

Preoperative optimization included packed red blood cell transfusions, correction of nutritional deficiencies and fluid and electrolyte abnormalities, when appropriate. Weaning-off steroids was aimed at, when possible. The main strategy was to discontinue biological therapy at least 4 weeks before surgery.

Surgical technique

The majority of patients had undergone a thorough preoperative gastrointestinal mapping with ileocolonoscopy and computed tomography or magnetic resonance enterography. All operations were performed by the same specialist colorectal surgeon. ICRs were performed using an open or laparoscopic approach, according to the patient's disease characteristics; laparoscopic surgery was preferred for single stenotic disease of the ileocecal region. Patients with penetrating disease and abscesses or complex fistulas, need for multiple bowel resections, previous laparotomies or inability to tolerate pneumoperitoneum due to comorbidities, were operated using an open approach. Regardless of the surgical approach, the resection included only the macroscopically diseased bowel segment, whereas the mesentery was dissected and ligated close to the intestinal wall. The anastomotic configuration was selected according to the intraoperative findings: an end-to-end, single layer, hand-sewn anastomosis (EEA) was performed for bowel edges of similar diameter; otherwise, a double layer, hand-sewn, side-to-side hand-sewn anastomosis (SSA) was preferred. The decision regarding concomitant intestinal resection was made according to preoperative evaluation and intraoperative findings. Strictureplasties were performed only for small bowel strictures. Chronic, high-dose steroid therapy, as well as severe intra-abdominal sepsis and malnutrition, were considered indications for anastomotic diversion.

POC

Early POC and mortality within 30 days after surgery were recorded. Intra-abdominal septic complications (IASC) included anastomotic leakage, intra-abdominal abscess and enterocutaneous fistula. Overall POC included, apart from IASC, postoperative ileus, urinary tract infection (UTI), respiratory tract infection (RTI), hemorrhage, wound infection, and unexplained fever. The aforementioned POC were documented by appropriate laboratory tests and/or imaging modalities. Lastly, the incidence of re-operation within 30 days was calculated. We evaluated possible risk factors for IASC and overall POC.

Statistical analysis

Categorical variables were represented as absolute and relative frequencies (%). Normality of distribution for quantitative variables was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Mean value (\pm standard deviation) was used to describe normally distributed variables, whereas non-normally distributed ones were presented as median (25th-75th interquartile range [IQR]). Univariate analysis was conducted using Pearson's chi-square test or Fisher's exact test to compare categorical variables, where appropriate. When statistical significance was reached in a 2x3 contingency table, a *post hoc* analysis was conducted using the Bonferroni adjustment for P-value. The independent samples *t*-test was used for the comparison of normally distributed continuous data, whereas the Mann-Whitney *U* test was used for non-parametrical variables. Multivariate analysis was conducted using a multiple logistic regression model for the calculation of odds ratio (OR) with 95% confidence interval (CI). All P-values were 2-sided and values <0.05 were considered statistically significant. All calculations were performed using SPSS version 23.0 software (SPSS, Chicago, IL).

Results

Baseline characteristics

The demographic, clinical and surgical characteristics of 153 patients are presented in Table 1. Our population had a median age of 36 years (IQR 28-47 years), and included 86 male patients (56.2%) and 61 active smokers (39.9%). Single ICR was performed in most cases (86.9%), whereas 20 patients underwent concomitant resection and/or strictureplasty. A laparoscopic approach was preferred in 19 patients (12.4%), whereas EEA was the most common anastomotic configuration (n=128, 83.7%). Severe anemia (hemoglobin [Hb] <8 g/dL) was not recorded in any patient and the majority of patients (86.5%) had serum albumin >3.0 g/dL. According to the ASA score, the study population had no severe comorbidities (ASA I/II, 93.5%). Most patients had no perianal involvement (77.1%) or previous resections (84.3%).

Preoperative medical treatment was described according to the kind of medication and therapeutic regimen; anti-TNF was the most commonly used category (39.9%), as either monotherapy (25.5%) or combination treatment (14.4%). Vedolizumab (3.3%) and ustekinumab (2.0%) were used only as monotherapy regimens. Steroid therapy was taken by 23.5% of patients. Homogeneity among patients who were under anti-TNF therapy or not was analyzed (Table 2). Statistically significant differences between the 2 groups were observed for median age (34 vs. 38.5 years, P=0.016), age at diagnosis according to Montreal classification (P=0.010), and steroid use, which was less frequent in anti-TNF patients (13.1% vs. 30.4%, P=0.013).

Table 1 Overall baseline characteristics (n=153)

| Characteristics | Value |
|---|----------------|
| Age (years), median (IQR) | 36 (28-47) |
| Male sex, n (%) | 86 (56.2) |
| Smoking, n (%) | 61 (39.9) |
| BMI (kg/m ²), mean \pm SD | 22.9 \pm 3.9 |
| <18.5, n (%) | 16 (10.9) |
| 18-25, n (%) | 89 (60.5) |
| 25-30, n (%) | 37 (25.2) |
| 30-35, n (%) | 4 (2.7) |
| >35, n (%) | 1 (0.7) |
| Hemoglobin (g/dL), mean \pm SD | 12.7 \pm 1.8 |
| No anemia, n (%) ^s | 65 (62.5) |
| Mild anemia, n (%) | 17 (16.3) |
| Moderate anemia, n (%) | 22 (21.2) |
| Severe anemia, n (%) | 0 (0) |
| Albumin (g/dL), median (IQR) | 3.7 (3.3-4.1) |
| >3.0, n (%) | 90 (86.5) |
| ASA Score I/II, n (%) | 143 (93.5) |
| Montreal – Age, n (%) | |
| A1, | 23 (15.0) |
| A2 | 101 (66.0) |
| A3 | 29 (19) |
| Montreal – Location, n (%) | |
| L1 | 92 (60.1) |
| L2 | 9 (5.9) |
| L3 | 52 (34.0) |
| Montreal - L4, n (%) | 4 (2.6) |
| Montreal – Behavior, n (%) | |
| B1 | 9 (5.9) |
| B2 | 95 (62.1) |
| B3 | 49 (32.0) |
| Perianal disease, n (%) | 35 (22.9) |
| Disease duration (years), median (IQR) | 7.2 (2.5-14.0) |
| <5, n (%) | 62 (40.5) |
| 5-10, n (%) | 36 (23.5) |
| >10, n (%) | 55 (35.9) |
| Extraintestinal manifestations, n (%) | 48 (31.4) |
| Previous resection, n (%) | 24 (15.7) |
| Laparoscopic approach, n (%) | 19 (12.4) |
| Procedure, n (%) | |
| ICR | 133 (86.9) |
| ICR + Strictureplasty | 5 (3.3) |
| ICR + resection | 13 (8.5) |
| ICR + resection + strictureplasty | 2 (1.3) |
| Anastomotic configuration, n (%) | |
| EEA | 128 (83.7) |
| SSA | 25 (16.3) |
| Medication, n (%) | |
| 5-ASA | 12 (7.8) |
| IM | 35 (22.9) |
| Steroids | 36 (23.5) |
| Anti-TNF | 61 (39.9) |
| Vedolizumab | 5 (3.3) |
| Ustekinumab | 3 (2.0) |

(Contd...)

Table 1 (Continued)

| Characteristics | Value |
|----------------------------|-----------|
| Therapeutic regimen, n (%) | |
| None | 44 (28.8) |
| Monotherapy | |
| IM | 12 (7.8) |
| Steroid | 19 (12.4) |
| Anti-TNF | 39 (25.5) |
| Vedolizumab | 5 (3.3) |
| Ustekinumab | 3 (2.0) |
| Combination therapy | |
| Steroid + IM | 9 (5.9) |
| Anti-TNF + IM | 14 (9.2) |
| Anti-TNF + Steroids | 8 (5.2) |

⁹World Health Organization classification; mild anemia when serum hemoglobin (Hb) 11-12 g/dL for females and 11-13 g/dL for males, moderate for Hb 8-11 g/dL and severe for Hb <8 g/dL (16)

IQR, interquartile range; BMI, body mass index; ASA, American Society of Anesthesiologists; ICR, ileocolic resection; EEA, end-to-end anastomosis; SSA, side-to-side anastomosis; 5-ASA, 5-aminosalicylic acid; TNF, tumor necrosis factor; IM, immunomodulators

POC

Overall, 35 patients (22.9%) experienced POC (Table 3). Anastomotic leakage was the most common POC (n=18, 11.8%) and IASC was recorded in 19 patients (12.4%). Postoperative ileus was the most frequent non-IASC complication (3.9%), while postoperative hemorrhage and unexplained fever were recorded in 4 patients (2.6%). Non-IASC septic complications included wound infections (2.0%), UTI (1.3%), and RTI (0.7%). In total, 22 patients required reintervention (14.4%); 17 with IASC (2 cases with anastomotic leak were treated conservatively), 4 with hemorrhage and 1 with postoperative bowel obstruction. No patient died during the 30-day postoperative period.

Univariate analysis

The analysis of preoperative medications showed no statistically significant differences in the rates of overall POC and IASC (Fig. 1). Steroid therapy was associated with a higher incidence of overall POC (33.3%), although statistical significance was not reached (P=0.09). Patients with preoperative administration of anti-TNF agents had a non-significantly lower percentage of overall POC (21.3% vs. 23.9%, P=0.71) and a non-significantly higher percentage of IASC (13.1% vs. 12.0%, P=0.83). Similarly, the analysis according to the therapeutic regimen revealed no significant differences in overall and IASC rates (Fig. 2). Anti-TNF treatment was not associated with overall POC or IASC, either as monotherapy or in combination regimens. The administration of steroids, either as monotherapy or as a combination treatment with IM or anti-TNF, showed the highest incidences of overall POC, although the differences were statistically non-significant (31.6%, P=0.35; 33.3%, P=0.41; 37.5%, P=0.37, respectively). As for IASC, combined steroid and anti-TNF therapy had the highest rate (25.0%, P=0.23). Patients under a combined

anti-TNF and IM regimen showed insignificantly lower percentages of complications (7.1%, P>0.99). The number of patients receiving vedolizumab (n=5) or ustekinumab (n=3) was too small for analysis.

Demographic, clinical and surgical variables were used in the univariate analysis (Table 4). Three variables were associated with significantly higher rates of overall POC and IASC: perianal disease (37.1%, P=0.022 and 25.7%, P=0.016, respectively), a history of previous intestinal resection (54.2%, P<0.001 and 37.5%, P<0.001, respectively), and disease duration (P=0.012 and 0.029, respectively). Statistical significance for the “disease duration” variable was noted after the *post hoc* analysis for patients with >10 years of diagnosed CD compared to those with <5 years (36.4% vs. 16.1%, P=0.012 for overall POC and 21.8% vs. 6.5%, P=0.016 for IASC).

Multivariate analysis

Preoperative medication variables and others with a P-value <0.25 in the univariate analysis were inserted into a binary logistic regression model (Table 5). Previous resections were the only significant independent predictor for overall POC and IASC: OR 3.90, 95%CI 1.38-11.06; P=0.010, and OR 4.56, 95%CI 1.51-13.77; P=0.007, respectively. In contrast to the univariate analysis, perianal disease and duration of CD >10 years were not independently associated with a higher OR for POC. Preoperative medication was also non-significantly correlated with POC.

Discussion

In this retrospective study we tried to detect and analyze risk factors for POC in a Greek cohort of CD patients operated in a high-volume tertiary center, paying special attention to the patients' preoperative immunosuppressive therapy. In total, 22.9% of our patients experienced some kind of POC; this finding is comparable with complication rates reported in other studies [15,18,19]. Anastomosis-related complications, usually presenting as free peritoneal leakage or intra-abdominal abscess leading to intra-abdominal sepsis, represent the category of POC causing most concern among colorectal-IBD surgeons. The recognition of patients at a higher risk for IASC is crucial and affects the surgical strategy; anastomotic dysfunction with a temporary stoma is the preferred option for these patients. In our series the incidence of IASC was 12.4%, also comparable with the current literature [17,20,21].

According to this study's findings, anti-TNF treatment within 3 months before surgery was not associated with a higher risk for overall POC or IASC. The great concern regarding the safety of anti-TNF agents is that their immense immunosuppressive effect could not only affect the patient's defense against infections, but theoretically impair the healing cascade as well, leading to septic and anastomotic complications. Clinical data from a large number of non-randomized, mainly

Table 2 Comparison of baseline characteristic between patients under anti-TNF therapy and not

| Characteristics | Anti-TNF (n=61) | No Anti-TNF (n=92) | P-value |
|--|-----------------|--------------------|---------|
| Age (years), median (IQR) | 34 (25 – 41.5) | 38.5 (31 - 49) | 0.016 |
| Male sex, n (%) | 33 (54.1) | 53 (57.6) | 0.67 |
| Smoking, n (%) | 20 (32.8) | 41 (44.6) | 0.15 |
| BMI (kg/m ²), mean ± SD | 22.7±4.3 | 23.1±3.7 | 0.54 |
| <18.5, n (%) | 8 (13.6) | 8 (9.1) | 0.08 |
| 18.5-25, n (%) | 35 (59.3) | 54 (61.4) | |
| 25-30, n (%) | 12 (20.3) | 25 (28.4) | |
| 30-35, n (%) | 4 (6.8) | 0 (0.0) | |
| >35, n (%) | 0 (0.0) | 1 (1.1) | |
| Hemoglobin (g/dL), mean ± SD | 12.5±1.8 | 12.9±1.9 | 0.31 |
| No anemia, n (%) [§] | 25 (59.5) | 40 (64.5) | 0.84 |
| Mild anemia, n (%) | 7 (16.7) | 10 (16.1) | |
| Moderate anemia, n (%) | 10 (23.8) | 12 (19.4) | |
| Severe anemia, n (%) | 0 (0.0) | 0 (0.0) | |
| Albumin (g/dL), median (IQR) | 3.7 (3.3-4.1) | 3.7 (3.4-4.0) | 0.67 |
| <3.0, n (%) | 7 (16.7) | 7 (11.3) | 0.43 |
| ASA Score I/II, n (%) | 57 (93.4) | 86 (93.5) | >0.99 |
| Montreal – Age, n (%) | | | 0.010 |
| A1 | 15 (24.6) | 8 (8.7) | |
| A2 | 39 (63.9) | 62 (67.4) | |
| A3 | 7 (11.5) | 22 (23.9) | |
| Montreal – Location, n (%) | | | 0.28 |
| L1 | 32 (52.5) | 60 (65.2) | |
| L2 | 4 (6.6) | 5 (5.4) | |
| L3 | 25 (41.0) | 27 (29.3) | |
| Montreal - L4, n (%) | 2 (3.3) | 2 (2.2) | >0.99 |
| Montreal – Behavior, n (%) | | | 0.76 |
| B1 | 3 (4.9) | 6 (6.5) | |
| B2 | 40 (65.6) | 55 (59.8) | |
| B3 | 18 (29.5) | 31 (33.7) | |
| Perianal disease, n (%) | 18 (29.5) | 17 (18.5) | 0.11 |
| Disease duration (years), median (IQR) | 8.8 (3.0-15.5) | 6.15 (2.0-12.0) | 0.08 |
| <5, n (%) | 21 (34.4) | 41 (44.6) | 0.33 |
| 5-10, n (%) | 14 (23.0) | 22 (23.9) | |
| >10, n (%) | 26 (42.6) | 29 (31.5) | |
| Extraintestinal manifestations, n (%) | 19 (31.1) | 29 (31.5) | 0.96 |
| Previous resection, n (%) | 13 (21.3) | 11 (12.0) | 0.12 |
| Laparoscopic approach, n (%) | 8 (13.1) | 11 (12.0) | 0.83 |
| Procedure, n (%) | | | 0.52 |
| ICR | 52 (82.0) | 83 (90.2) | |
| ICR + Strictureplasty | 3 (4.9) | 2 (2.2) | |
| ICR + resection | 7 (11.5) | 6 (6.5) | |
| ICR + resection + strictureplasty | 1 (1.6) | 1 (1.1) | |
| Anastomotic configuration, n (%) | | | 0.65 |
| EEA | 50 (82.0) | 78 (84.8) | |
| SSA | 11 (18.0) | 14 (15.2) | |
| Medication, n (%) | | | |
| 5-ASA | 4 (6.6) | 8 (8.7) | 0.76 |
| IM | 14 (23.0) | 21 (22.8) | 0.99 |
| Steroids | 8 (13.1) | 28 (30.4) | 0.013 |

[§] World Health Organization classification; mild anemia when serum hemoglobin (Hb) 11-12 g/dL for females and 11-13 g/dL for males, moderate for Hb 8-11 g/dL and severe for Hb <8 g/dL (16)

IQR, interquartile range; TNF, tumor necrosis factor; BMI, body mass index; ASA, American Society of Anesthesiologists; ICR, ileocolic resection; EEA, end-to-end anastomosis; SSA, side-to-side anastomosis; 5-ASA, 5-aminosalicylic acid; IM, immunomodulators

retrospective studies are conflicting. Some are in accordance with our findings, concluding that preoperative anti-TNFs significantly correlate with POC [22-24]. A multicenter retrospective study with 231 patients found that overall complications, anastomotic leak and IASC rates were not

increased in patients under infliximab or adalimumab [17]. Furthermore, a nationwide prospective study from the REMIND group assessed the impact of anti-TNF agents by evaluating the preoperative serum trough levels; it was found that POC were not increased, regardless of the interval from last dosing or the serum levels before surgery [15]. Similarly, recently published data from another multicenter prospective cohort (PUCCINI trial) with 955 IBD patients, although not separating patients with CD from those with ulcerative colitis (UC), showed that anti-TNF medication within 3 months preoperatively was not an independent predictor for infectious complications, even when there were detectable serum drug levels at the time of surgery [25].

On the other hand, many studies have documented an increased risk for postoperative morbidity, especially septic POC [26,27]. Recent retrospective data from Leuven and Amsterdam, concerning 538 patients who had undergone ileocecal resection, reported an OR of 3.30 (95%CI 1.09-9.99, P=0.035) for anastomotic leakage for patients receiving anti-TNF medication [19]. In 2018, a prospective study of a nationwide cohort of 592 patients from France was published, in which anti-TNF within 3 months before ICR was an independent risk factor for overall POC [28]. Similarly, Kulaylat et al analyzed a large database of 2364 patients, adjusting for confounders such as emergency surgery, and concluded that

Table 3 Postoperative complications

| Complications | n (%) |
|------------------------------------|-----------|
| Overall | 35 (22.9) |
| IASC | 19 (12.4) |
| Anastomotic leak | 18 (11.8) |
| Intra-abdominal collection/abscess | 1 (0.7) |
| Other | |
| Postoperative ileus | 6 (3.9) |
| Hemorrhage | 4 (2.6) |
| Unexplained fever | 4 (2.6) |
| Wound infection | 3 (2.0) |
| UTI | 2 (1.3) |
| RTI | 1 (0.7) |
| Deaths | 0 (0.0) |
| Reoperation | 22 (14.4) |

IASC, intra-abdominal septic complication; UTI, urinary tract infection; RTI, respiratory tract infection

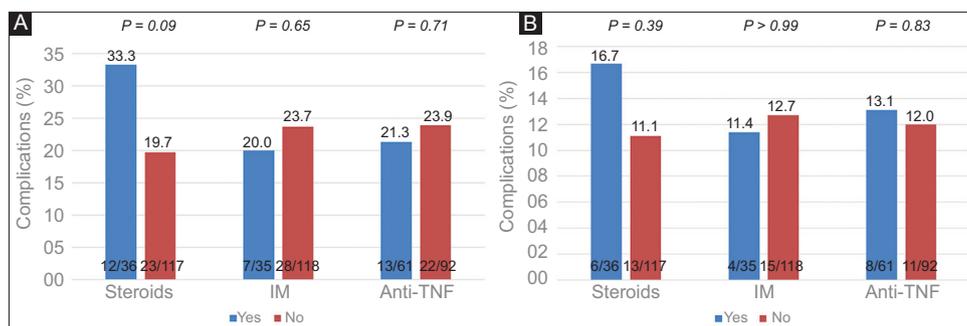


Figure 1 Univariate analysis for the correlation of overall (A) and intra-abdominal septic (B) postoperative complications with preoperative medication

IM, immunomodulators; TNF, tumor necrosis factor

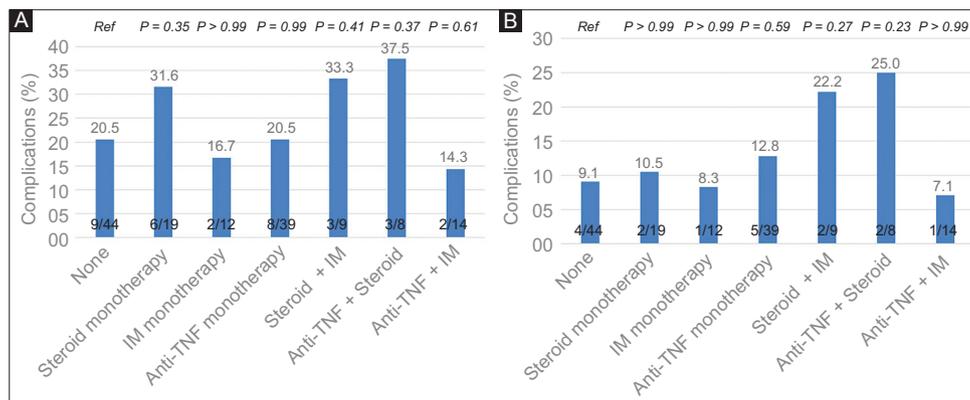


Figure 2 Univariate analysis for the correlation of overall (A) and intra-abdominal septic (B) postoperative complications with preoperative therapeutic regimen. All P-values are vs. none. Overall P=0.75 (A) and 0.80 (B)

IM, immunomodulators; TNF, tumor necrosis factor

Table 4 Univariate analysis for detection of risk factors for postoperative complications

| Risk factors | n | Overall complications (n=35) | P-value | IASC (n=19) | P-value |
|---------------------------------------|-----|------------------------------|---------------------|--------------------------|----------------------|
| Age (years), median (IQR) | 153 | 39 (28-48) vs 35 (28-46) | 0.43 | 40 (35-48) vs 35 (28-47) | 0.34 |
| Male sex, n (%) | | | 0.79 | | 0.41 |
| Yes | 86 | 19 (22.1) | | 9 (10.5) | |
| No | 67 | 16 (23.9) | | 10 (14.9) | |
| Smoking, n (%) | | | 0.23 | | 0.23 |
| Yes | 61 | 17 (27.9) | | 10 (16.4) | |
| No | 92 | 18 (19.6) | | 9 (9.8) | |
| BMI (kg/m ²), mean ± SD | | | 0.79 | | 0.73 |
| <18.5, n (%) | 16 | 4 (25.0) | | 3 (18.8) | |
| 18.5-25, n (%) | 89 | 22 (24.7) | | 12 (13.5) | |
| 25-30, n (%) | 37 | 8 (21.6) | | 3 (8.1) | |
| 30-35, n (%) | 4 | 0 (0.0) | | 0 (0.0) | |
| >35, n (%) | 1 | 0 (0.0) | | 0 (0.0) | |
| Anemia, n (%) ^s | | | 0.95 | | 0.74 |
| Yes | 39 | 8 (20.5) | | 3 (7.7) | |
| No | 65 | 13 (20.0) | | 7 (10.8) | |
| Albumin >3.0 g/dL, n (%) | | | 0.47 | | 0.62 |
| >3.0, n (%) | 90 | 17 (18.9) | | 8 (8.9) | |
| <3.0, n (%) | 14 | 4 (28.6) | | 2 (14.3) | |
| ASA Score, n (%) | | | 0.70 | | 0.36 |
| I/II | 143 | 32 (22.4) | | 17 (11.9) | |
| III - IV | 10 | 3 (30.0) | | 2 (20.0) | |
| Montreal – Age, n (%) | | | 0.43 | | 0.14 |
| A1 | 23 | 6 (26.1) | | 5 (21.7) | |
| A2 | 101 | 25 (24.8) | | 13 (12.9) | |
| A3 | 29 | 4 (13.8) | | 1 (3.4) | |
| Montreal – Location, n (%) | | | 0.72 | | 0.55 |
| L1 | 92 | 21 (22.8) | | 12 (13.0) | |
| L2 | 9 | 3 (33.3) | | 2 (22.2) | |
| L3 | 52 | 11 (21.2) | | 5 (9.6) | |
| Montreal – L4, n (%) | | | 0.57 | | >0.99 |
| Yes | 4 | 0 (0.0) | | 0 (0.0) | |
| No | 149 | 35 (23.5) | | 19 (12.8) | |
| Montreal – Behavior, n (%) | | | 0.74 | | 0.99 |
| B1 | 9 | 3 (33.3) | | 1 (11.1) | |
| B2 | 95 | 21 (22.1) | | 12 (12.6) | |
| B3 | 49 | 11 (22.4) | | 6 (12.2) | |
| Perianal disease, n (%) | | | 0.022 | | 0.016 |
| Yes | 35 | 13 (37.1) | | 9 (25.7) | |
| No | 118 | 22 (18.6) | | 10 (8.5) | |
| Disease duration (years), n (%) | | | 0.012 ^{ss} | | 0.029 ^{sss} |
| <5 | 62 | 10 (16.1) | | 4 (6.5) | |
| 5-10 | 36 | 5 (13.9) | | 3 (8.3) | |
| >10 | 55 | 20 (36.4) | | 12 (21.8) | |
| Extraintestinal manifestations, n (%) | | | 0.99 | | 0.11 |
| Yes | 48 | 11 (22.9) | | 9 (18.8) | |
| No | 105 | 24 (22.9) | | 10 (9.5) | |
| Previous resection, n (%) | | | <0.001 | | <0.001 |
| Yes | 24 | 13 (54.2) | | 9 (37.5) | |
| No | 129 | 22 (17.1) | | 10 (7.8) | |

(Contd...)

Table 4 (Continued)

| Risk factors | n | Overall complications (n=35) | P-value | IASC (n=19) | P-value |
|-----------------------------------|-----|------------------------------|---------|-------------|---------|
| Laparoscopic approach, n (%) | | | 0.57 | | 0.71 |
| Yes | 19 | 3 (15.8) | | 3 (15.8) | |
| No | 134 | 32 (23.9) | | 16 (11.9) | |
| Procedure, n (%) | | | 0.78 | | 0.88 |
| ICR | 133 | 30 (22.6) | | 16 (12.0) | |
| ICR + Strictureplasty | 5 | 1 (20.0) | | 1 (20.0) | |
| ICR + resection | 13 | 4 (30.8) | | 2 (15.4) | |
| ICR + resection + strictureplasty | 2 | 0 (0.0) | | 0 (0.0) | |
| Anastomotic configuration, n (%) | | | 0.88 | | 0.32 |
| EEA | 128 | 29 (22.7) | | 18 (14.1) | |
| SSA | 25 | 6 (24.0) | | 1 (4.0) | |

⁹ World Health Organization classification; anemia is defined when serum hemoglobin <12 g/dL for females and <13 g/dL for males (16)

⁹⁶ Post hoc analysis: <5 years vs. 5-10 years, P=0.77; <5 years vs. >10 years, P=0.012; 5-10 years vs. >10 years, P=0.019. P-values of <0.017 were considered statistically significant according to the Bonferroni correction

⁹⁸ Post hoc analysis: <5 years vs. 5-10 years, P=0.71; <5 years vs. >10 years, P=0.016; 5-10 years vs. >10 years, P=0.09. P-values of <0.017 were considered statistically significant according to the Bonferroni correction

IASC, intra-abdominal septic complications; IQR, interquartile range; TNF, tumor necrosis factor; BMI, body mass index; ASA, American Society of Anesthesiologists; ICR, ileocolic resection; EEA, end-to-end anastomosis; SSA, side-to-side anastomosis; 5-ASA, 5-aminosalicylic acid; IM, immunomodulators

Table 5 Multivariate analysis for possible risk factors

| Risk factors | Overall complications Odds ratio (95%CI) | P-value | IASC Odds ratio (95%CI) | P-value |
|--------------------------------|--|---------|-------------------------|---------|
| Smoking | | | | |
| No | Ref | | Ref | |
| Yes | 1.44 (0.61 – 3.39) | 0.40 | 1.44 (0.60 – 3.47) | 0.41 |
| Montreal – Age | | | | |
| A1 | - | | Ref | |
| A2 | - | | 1.01 (0.29 – 3.49) | 0.99 |
| A3 | - | | 0.45 (0.08 – 2.40) | 0.35 |
| Perianal disease | | | | |
| No | Ref | | Ref | |
| Yes | 1.95 (0.74 – 5.16) | 0.18 | 1.79 (0.66 – 4.88) | 0.26 |
| Disease duration (years) | | | | |
| <5 | Ref | | Ref | |
| 5-10 | 0.93 (0.28 – 3.11) | 0.91 | 0.82 (0.24 – 2.86) | 0.76 |
| >10 | 1.94 (0.74 – 5.11) | 0.18 | 1.76 (0.65 – 4.77) | 0.27 |
| Extraintestinal manifestations | | | | |
| No | - | | Ref | |
| Yes | - | | 0.72 (0.28 – 1.82) | 0.48 |
| Previous resection | | | | |
| No | Ref | | Ref | |
| Yes | 3.90 (1.38 – 11.06) | 0.010 | 4.56 (1.51 – 13.77) | 0.007 |
| Steroids | | | | |
| No | Ref | | Ref | |
| Yes | 1.99 (0.78 – 5.13) | 0.15 | 1.91 (0.72 – 5.03) | 0.19 |
| IM | | | | |
| No | Ref | | Ref | |
| Yes | 0.78 (0.28 – 2.19) | 0.64 | 0.72 (0.25 – 2.03) | 0.53 |
| Anti-TNF | | | | |
| No | Ref | | Ref | |
| Yes | 0.72 (0.29 – 1.81) | 0.49 | 0.64 (0.25 – 1.68) | 0.37 |

CI, confidence interval; IASC, intra-abdominal septic complications; IM, immunomodulators; TNF, tumor necrosis factor

the overall and septic POC are significantly higher in anti-TNF exposed patients [18].

A critical question is whether a surgeon should postpone an elective surgery according to the timing of the last drug infusion. Since evidence for the safety of anti-TNFs is conflicting, our practice was to perform elective ICRs when a period of at least 4 weeks had elapsed since the last administration of anti-TNF; we could assume that this time interval seems to be safe. A Danish nationwide cohort with 2293 CD patients concluded that anti-TNF administration within 14 days before surgery was not associated with a higher risk for POC compared to longer intervals [22]. A meta-analysis conducted for the comparison of different time intervals (within 4, 8 and 12 weeks) also found no significant differences [29]. Lau *et al*, in contrast to the PUCINI trial and the prospective cohort from the REMIND group, found that anti-TNF serum levels at surgery of ≥ 3 $\mu\text{g/mL}$ correlated with increased overall postoperative morbidity and infectious complications, while levels of ≥ 8 $\mu\text{g/mL}$ correlated with overall postoperative morbidity and readmissions [30]. Nevertheless, in this study a major limitation was that data regarding the interval between last infusion and surgery were not obtained and therefore the optimal timing for last dosing could not be estimated. Overall, it seems that the preoperative serum levels of the drug do not help discriminate patients at risk and a safe time interval from last administration to surgery cannot be defined.

To date, since the conduction of well-designed randomized controlled trials is an unmet need because of ethical considerations, the literature provides clinicians with conflicting evidence about the perioperative safety of anti-TNF agents. This heterogeneity is reflected in the discrepancy of results from several meta-analyses that used the same pool of data. An interesting meta-analysis in 2013, by El-Hussuna *et al*, found a 1.6-fold increase in relative risk for anastomotic complications only when the analysis included studies with a low risk of bias [31]. Yang *et al* found an increased risk for overall and infectious complications in their meta-analysis and stated that the most appropriate definition with lower heterogeneity among studies would be infectious and non-infectious POC [32]. As for IASC, Huang in 2014 found that steroid use, hypoalbuminemia, previous surgery and preoperative abscess were predictors, but anti-TNF treatment was not [33]. In a 2018 meta-analysis with separate analysis for every category of POC described in previous studies (overall, major/minor, septic/non-septic, surgical/medical) anti-TNFs were not associated with any kind of POC [34], whereas a more recent study in 2019, which included 7115 patients, concluded that there is a higher risk for infectious POC [35]. The European Crohn's and Colitis Organization published in 2020 the updated guidelines for CD, stating that current evidence does not support any correlation of anti-TNF agents with POC after abdominal surgery [36].

In the present study, none of the other medications had a significant impact on POC. However, we detected a trend for increased overall POC in patients under steroid treatment, with borderline significance ($P=0.09$). Nevertheless, this finding is biased by the fact that patients under high doses of steroids for a long period and who needed ICR were protected by a diverting ileostomy and were thus excluded from this cohort. The dose-related association of steroids with POC

is definite [7,37]. Moreover, we tried to evaluate the effect of combined immunosuppressive therapy, but statistical significance was not reached for any possible combination of anti-TNFs, steroids and immunomodulators. However, there was a trend for increased overall POC and IASC when steroids were added to any other class of medication (Fig. 2). In accordance with our results, the REMIND Group study documented no association of anti-TNFs in combination with other immunosuppressants [15]. A recent large retrospective study found that double immunosuppression of steroids and biologicals was an independent risk factor for IASC [38]. Furthermore, McKenna's cohort in 2018 recorded an increased risk for IASC only with triple immunosuppression [16]. The 2 last studies included anti-TNFs as well as vedolizumab and ustekinumab as the "biological part" of the combined regimen; therefore, they could not conclude if a specific biological class, when combined, increased the risk. In our cohort, no patient was under a triple immunosuppressive regimen.

A history of previous resections was the only independent risk factor for overall POC and IASC in this cohort. The correlation of repeated resections with postoperative morbidity is not well documented in the literature. A multicenter retrospective study was the first to report this variable as an independent risk factor, but only for anastomotic leakage and not for IASC [17]. A subsequent single-center study by Johnston *et al* tried to confirm this finding and, although statistical significance was reached in univariate analysis, multivariate analysis was not conducted because of the limited data [39]. Our results are in accordance with 2 large, recently published, retrospective studies by the same team in the Mayo Clinic that documented previous resections as an independent risk factor for IASC [16,38]. Interestingly, this finding was confirmed by Huang's abovementioned meta-analysis in 2015, although none of the included studies reported previous surgery as a risk factor for IASC [33]. We therefore believe that our findings increase the evidence for the negative effect of previous resections on the postoperative course of CD patients. We speculate that this association could be attributed to the technical difficulties encountered in a previously operated abdomen, which could compromise the blood supply in bowel cut edges, in combination with the aggressive disease pattern in patients who require reoperations; both could impair anastomotic healing.

In the present cohort, patients were operated in the elective setting and were therefore adequately optimized with proper anemia and malnutrition management. The mean Hb concentration was 12.7 g/dL, with no difference between the "anti-TNF" and "no anti-TNF" groups, whereas no patient had severe anemia. Similarly, 86.5% of patients had serum albumin >3 g/dL and 89.1% of them BMI >18.5 kg/m². Thus, anemia and malnutrition were not confirmed as established risk factors [6,20,21]. Anastomotic technique is a controversial risk factor in the literature; current evidence, although weak, supports the superiority of a stapled SSA configuration over the EEA in terms of lower risk for anastomotic leak [36]. In our study, EEA was the prevailing configuration, all anastomoses were hand-sewn and differences between EEA and SSA were not confirmed for either overall POC or IASC. Last, the penetrating-B3 phenotype as a predictor was also not

confirmed [20,33]; patients with severe intra-abdominal sepsis and abscesses were either drained percutaneously or diverted.

This study has certain limitations that should be highlighted. First, the retrospective, single-center design and the consequent selection bias is a flaw. Furthermore, our population was not completely homogenous between anti-TNF and non-anti-TNF patients in terms of age, disease duration and steroid medication. Second, adjustment for certain confounders, such as disease activity, was not feasible. Although inclusion criteria were selected in order to include CD patients with mild disease, non-septic and under proper optimization strategy, disease severity data with validated scores might be useful. Last, although a (probably arbitrary) minimum interval of 4 weeks before elective surgery was kept as a rule of thumb, precise data could not be obtained regarding the last administration of anti-TNFs in order to include it as a variable in our analysis. However, we believe that this study adds more evidence in the evolving problem of POC in CD patients.

In conclusion, in the present study, previous resection was an independent risk factor for overall POC and IASC after elective ileocelectomy, adding more evidence about this variable to the existing literature. Preoperative medications, focusing especially on patients exposed to anti-TNF drugs, were not associated with postoperative morbidity, either as monotherapy regimens or as immunosuppressive combination treatments. Thus, we believe that a surgeon should take into account all possible risk factors for POC and should try to optimize the patient, rather than postpone an elective resection considering only the anti-TNF therapy status.

Summary Box

What is already known:

- The rates of postoperative complications (POC) and intra-abdominal septic complications (IASC) after ileocolic resection (ICR) for Crohn's disease are high
- The impact of anti-tumor necrosis factor (TNF)- α agents on POC and IASC remains debatable
- Highly consistent risk factors for POC are chronic, high-dose steroid therapy, poor nutritional status, anemia, complicated disease, and surgery in the emergency setting

What the new findings are:

- Preoperative administration of anti-TNF agents, either as monotherapy or in combination with other immunosuppressants, did not correlate with the total POC or IASC in patients undergoing elective ICR with primary anastomosis
- The history of previous intestinal resection was associated with significantly higher rates of total POC and IASC

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